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Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands

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Objective To compare the prescription of drugs in women over a period from 2 years before until 3 months after pregnancy, regarding the type of drugs used and the fetal risk.

Design A cohort study based on pharmacy records of women giving birth to a child between 1994 and 2003.

Setting The study was performed with data from the InterAction database, containing prescription-drug-dispensing data from community pharmacies.

Population The study population included 5412 women for whom complete pharmacy records were available.

Methods Drugs were classified into three categories: (1) drugs for chronic conditions, (2) drugs for occasional use and (3) drugs for pregnancy-related symptoms and also classified according to the Australian classification system.

Main outcome measures The prescription rate was calculated as the number of women per 100 women who received one or more prescriptions for a given drug within a specified time period.

Results About 79.1% of the women received at least one prescription during pregnancy. The prescription rate for most drugs for chronic diseases and for occasional use decreased during pregnancy, whereas, as expected, the prescription rate for pregnancy-related drugs increased. During the first trimester of pregnancy, 1.7% of all drugs prescribed for chronic conditions and 2.3% of the occasional drugs were classified as harmful.

Conclusions The increase in prescription rate during pregnancy is caused by an increase in prescription rate of drugs for pregnancy-related symptoms. The prescription of harmful drugs is more commonly associated with drugs for occasional use rather than with drugs for chronic conditions. Therefore, a more cautious prescribing of drugs to healthy women in the fertile age is necessary.

Keywords Drug utilisation, fetal risk classification, pregnancy, prescription rate, register based.

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Introduction

Since the teratogenic risk of most drugs is still undetermined, it is important to monitor drug use regularly among pregnant women. Drug-utilisation studies reveal that most women use drugs during pregnancy, with estimations varying from 44[1] to 99%.[2] However, comparison is difficult because of differences in study design. Interviews or prescription databases may be used for collecting drug-use data, and the type of drugs studied may or may not include over-the-counter (OTC) drugs such as vitamins, iron and analgesics. Most studies found an increasing trend in drug use during pregnancy.[2–7]

Drug use cannot be always avoided during pregnancy. For women with certain chronic medical conditions such as epilepsy, diabetes, inflammatory bowel disease and asthma, the use of drugs is essential, and benefits for mother and child may well outweigh the teratogenic risk of the drug.[8,9] Other nonchronic diseases related or unrelated to the pregnancy may require medical treatment. Most studies do not distinguish between the different reasons for which the drugs are

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prescribed. Therefore, it is not clear to what extent changes in drug use among pregnant women can be explained by chronic, occasional or pregnancy-related drug use.

The aim of this study was to compare the prescription of drugs in pregnant women, with respect to the type of drugs and the fetal risk before, during and after pregnancy.

Methods

This study was performed with the InterAction database (IADB), which contains data on prescriptions dispensed from community pharmacies in the Netherlands. The IADB includes all prescription drugs from an estimated population of 220 000 from 1994 to 1999 and was expanded to approximately 450 000 since 1999.[10,11] Registration is irrespective of health insurance and is considered representative for the general population. Each prescription record contains information about the drug, date of dispensing, quantity dispensed, dose regimen and the prescribing physician. The indication for the prescription is not known. All the drugs are coded according to Anatomical Therapeutic Chemical (ATC) classification.[12] Each patient has a unique (anonymous) identifier; date of birth and gender of patients are known. Due to a high patient–pharmacy commitment in the Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete.[13] The IADB does not include OTC drugs and drugs dispensed during hospitalisations.

To identify mothers, all children born between 1 January 1994 and 1 January 2004 were selected from the database. For each child within the IADB, the female person 15–50 years older than the child with the same address code was considered to be the mother, providing there were no other female persons 15–50 years older with the same address code. Using this method, 65% of the mothers could be identified. Validation of this method is described in detail by Schirm *et al.*[14] Because only the child's birth date is known, the theoretical conception date was determined as the date of birth minus 273 days (i.e. 9 months). Between 1 January 1994 and 1 January 2004, 10 261 women were identified, with a total of 13 894 pregnancies. To rule out the influence of previous pregnancies, we included only the first pregnancy, as registered in the database, for which complete pharmacy records were available in the IADB from 2 years before the theoretical conception date until 3 months after delivery. According to these criteria, 5501 women were included. To avoid misclassification of medication use, we subsequently excluded women who gave birth to twins ($n = 87$) or triplets ($n = 2$) because the gestation period in twin and triplet pregnancies is more likely to be shorter than in singleton pregnancies. Thus, for the final analysis, pharmacy data for 5412 women were used. To allow direct comparisons of prescription rates over time, the whole study period of 3 years was divided into 12 periods of 13 weeks (trimesters). The 12 trimesters were numbered as can be seen in Figure 1.

We ordered drugs that were commonly prescribed into three mutually exclusive categories: (1) drugs for chronic conditions, (2) drugs for occasional and short-time use and (3) drugs for pregnancy-related symptoms. Drugs and drug groups belonging to these three categories are listed in Table 1. Drugs for chronic conditions are not necessarily taken on a chronic basis but can also be taken during episodes when the disease surfaces. The drugs were also classified based on the Australian risk classification for pregnancy (Table 2).[15] Categories D and X were combined because for both categories, the use of drugs during pregnancy is clearly contraindicated and only one drug was classified as X (isotretinoine, D10BA01). The three B categories were combined for statistical purposes. Drugs that were not classified according to the Australian classification system were categorised as B because their fetal risk was obviously unknown.

Per trimester, we counted the number of specific drugs prescribed to individual women, excluding contraceptives. If a specific drug was prescribed twice during a trimester, it was counted only once. In addition, prescriptions covering more than one trimester were counted only in the trimester in which they were dispensed. The prescription rate was calculated as the number of women per 100 women who received one or more prescriptions for a given drug or drug class within one trimester or otherwise specified time period. Prescription rates were tested in SPSS 12.0.2 for Windows (Chicago, USA) over the 3-year study period and the pregnancy period, using the chi-square test for trend.

Results

The mean age at birth of the 5412 mothers included was 29.6 years (range 15–49 years). During the 3-year study period, they received a total of 78 944 drugs, excluding contraceptives, of

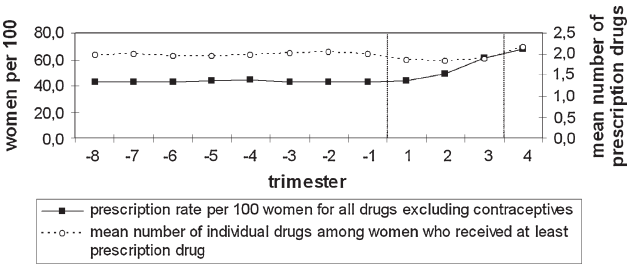

Figure 1. Prescription rate for all prescriptions and the mean number of drugs dispensed among women with at least one prescription. Trimester –8 to –5 represents the second year before pregnancy, trimester –4 to –1 represents the first year before pregnancy. The period between the dotted lines (trimester 1–3) is the pregnancy period, and trimester 4 is the period after pregnancy.

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Table 1. Categorisation of drugs and drug groups included in this study, according to their ATC code

Categories	ATC code
Category I: Drugs for chronic conditions	
Drugs used in diabetes	A10
Corticosteroids, dermatological preparations	D07
Corticosteroids for systemic use	H02
Thyroid therapy	H03
Anti-inflammatory and antirheumatic products	M01
Antimigraine medication	N02C
Antiepileptics	N03A
Antipsychotics	N05A, excl. N05AB04
Antidepressants	N06A
Antiasthmatics	R03
Category II: Drugs for occasional and short-time use	
Antispasmodic and anticholinergic agents and propulsives	A03, excl. A03FA01
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents	A07
Antifungals for dermatological use	D01
Emollients and protectives	D02
Antibiotics and chemotherapeutics for dermatological use	D06
Antiacne preparations	D10
Antibacterials for systemic use	J01
Analgesics and antipyretics	N02B
Anxiolytics	N05B
Hypnotics and sedatives	N05C
Antiparasitic products, insecticides and repellents	P
Antihistamines for systemic use	R06, excl. R06AD and R06AE
Ear, eye, nose and throat preparations	S02, S03, S01, R01, R02A, R05
Category III: Pregnancy-related drugs	
Antacids	A02A
Antiemetics	A03FA01, A04A, N05AB04, R06AD, R06AE
Laxatives	A06
Iron preparations	B03A
Folic acid and derivatives	B03B
Gynaecological anti-infectives and antiseptics	G01
Gonadotrophins and other ovulation stimulants	G03G

The drug categories are mutually exclusive.

which 12 407 drugs were dispensed during pregnancy. Overall, 5236 women (96.7%) received at least one prescription drug during the 3-year study period and 4280 (79.1%) received at least one prescription drug during their pregnancy. Figure 1 presents the prescription rates per trimester for all drugs, excluding contraceptives. In the 2 years before pregnancy, the prescription rate was constant, approximately 43 per 100 women. The average number of drugs per trimester among women who were prescribed drugs was two (range 1–17). The prescription rate increased from 43.6 per 100 women in the first trimester to 49.3 and 60.8 per 100 women in the second and third trimester of pregnancy. During pregnancy, the mean number of prescription drugs per trimester among women who were prescribed drugs was approximately the same as before pregnancy (1.9).

During the 3-year study period, 865 different drugs (based on ATC code) were prescribed to our study population, while during the pregnancy period, 470 different drugs were prescribed. The drugs categorised in Table 1 accounted for 57.3% of all the different drugs prescribed and for 81.9% of all prescriptions during the 3-year study period. For the pregnancy period, these were 65.7 and 89.1%, respectively.

The prescription rates per trimester for the drugs listed in Table 1 are reported in Appendix 1. A graphical reproduction of the prescription patterns for certain drug groups of the three categories is shown in Figures 2–4.

A clear decrease in prescription rate in pregnancy was seen for antidepressants and antipsychotics (N06A/N05A), antimigraine drugs (N02C; Figure 2), anti-inflammatory and antirheumatic drugs (M01). The prescription rates for antiepileptics (N03A; Figure 2), antiasthmatics (R03) were nearly constant during pregnancy. There seems to be an increase in prescription rate for insulins (A10; Figure 2), but this was not statistically significant.

Table 2. Risk classification based on the Australian risk classification[15] and as used in this study

Category	Description	Fetal risk classification in this study
A	Drugs that have been taken by a large number of pregnant women and women of childbearing age, without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.	Safe
B	Drugs that have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage or have shown evidence of an increased occurrence of fetal damage, of which the significance is considered uncertain in humans.	Undetermined
C	Drugs that, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate, without causing malformations. These effects may be reversible.	Potentially harmful
D/X	Drugs that have caused or suspected to have caused or may be expected to cause an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.	Harmful

The prescription rates of drugs for occasional use generally showed a decrease during pregnancy, followed by an increase after delivery. For antibiotics (J01; Figure 3), there was a decrease in prescription rate in the first trimester in pregnancy but an increasing pattern in the second and third trimester. For antispasmodic and anticholinergic agents (A03) and for antihistamines for systemic use (R06), there was a decrease in prescription rate during pregnancy. For analgesics (N02B, Figure 3), hypnotics and anxiolytics (N05C/N05B) and for ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05; Figure 3), there was a decreasing trend during the 3-year period but constant rates during pregnancy.

As expected, the prescription patterns of drugs for pregnancy-related symptoms showed an increase during pregnancy. For folic acid and derivatives (B03B) and for antiemetics (A03FA01, A04A, R06AD, R06AE; Figure 4), the highest rates can be seen in the first trimester. Iron preparations (B03A), antacids (A02A; Figure 4) and gynaecological anti-infectives (G01; Figure 4) were most prescribed in the second and third trimester in pregnancy. The prescription of laxatives (A06) was highest after pregnancy. Ovulation stimulants (G03G) were most prescribed before pregnancy, with a prescription rate of 4.2 per 100 women.

Figures 5–7 show the distribution of the fetal risk classification of the prescribed drugs. In these figures, we included only the drugs that were ordered in the three categories according to Table 1. The corresponding numbers can be found in Appendix 2. As previously described, there was a clear decrease in the total number of prescribed drugs for chronic conditions (Figure 5) and for occasional and short-time use (Figure 6) during pregnancy. This decrease was in contrast with the number of prescribed drugs for pregnancy-related

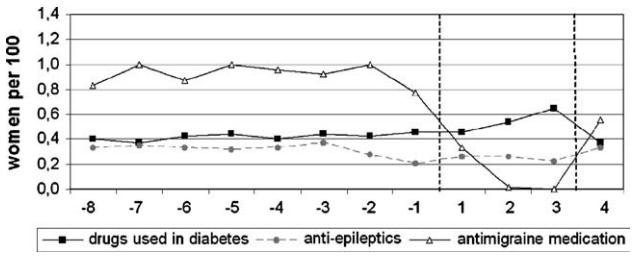

Figure 2. Prescription patterns for certain drugs for chronic conditions in the period from 2 years before pregnancy until 3 months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorisation of drug groups according to Table 1: drugs used in diabetes (A10), antimigraine medication (N02C) and antiepileptics (N03A).

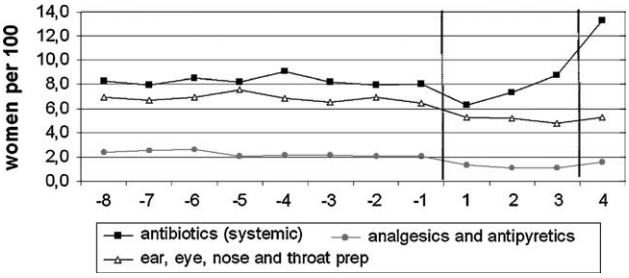

Figure 3. Prescription patterns for certain drugs for occasional and short-time use in the period from 2 years before pregnancy until 3 months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorisation of drug groups according to Table 1: antibacterials for systemic use (J01), analgesics and antipyretics (N02B) and ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05).

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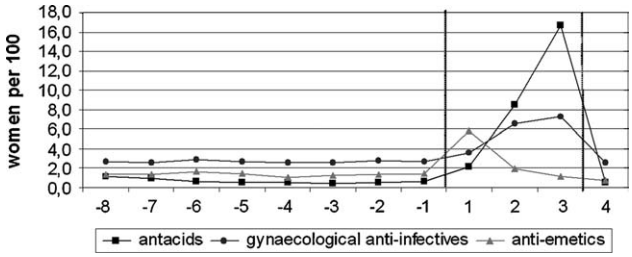

Figure 4. Prescription patterns for certain drugs for pregnancy-related symptoms in the period from 2 years before pregnancy until 3 months after delivery. The dots represent the prescription rate per trimester for the specific drug class. The period between dotted lines is the pregnancy period. Categorisation of drug groups according to Table 1: antacids (A02A), gynaecological anti-infectives and antiseptics (G01) and antiemetics (A03FA01, A04A, N05AB04, R06AD and R06AE).

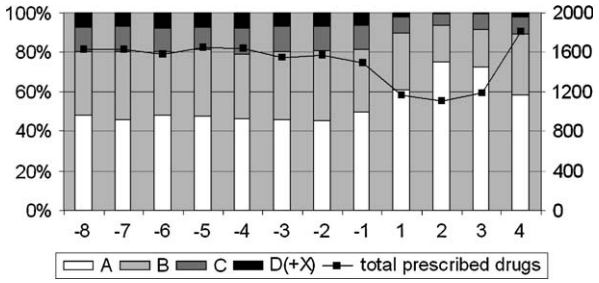

Figure 6. Total number of prescription drugs for occasional and short-time use (only the prescribed drugs that were categorised as drugs for occasional and short-time use as presented in Table 1 were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

symptoms, which showed a large increase during pregnancy, as shown in Figure 7. When taking all categories together, 81.7% of all drugs prescribed during pregnancy were classified as A, 10.9% as B, 6.3% as C and 1.1% as D or X. For the drugs prescribed during the first trimester, these percentages were 70.9, 16.5, 10.2 and 2.4, respectively. However, when we investigated the distribution of the prescribed drugs per category (chronic, occasional or pregnancy related), large differences are observed.

In the first trimester, only 50.4% of the prescribed drugs for chronic diseases were considered safe (A), 30.8% were potentially harmful (C) and 1.7% were classified as harmful (D or X). During pregnancy, the proportion of class A drugs increased to 67% in the third trimester and the proportion of drugs classified as C decreased to less than 15%. The proportion of harmful drugs was constant (1.9% in the third trimester). After pregnancy, the proportion of potentially harmful and harmful drugs increased to 45%. When we investigated the prescribed drugs for occasional and short-time use, 60.8% of the drugs in the first trimester were classified as safe, 7.8% as potentially harmful and 2.3% as harmful. During pregnancy, the proportion of drugs classified as A increased to over 70% in the second and third trimester. The proportion of harmful drugs decreased to 0.4% in the third trimester. The majority of the drugs prescribed for pregnancy-related symptoms in the first trimester were classified as safe, 2.1% as potentially harmful and 2.9% as harmful. In the second and third trimester of pregnancy, 97.6% of the drugs prescribed for pregnancy-related symptoms were classified as A, 1% as C and 0.2% as D or X.

Discussion

A clear change in drug prescription patterns is visible among pregnant women in the Netherlands. Drugs for chronic conditions and for occasional and short-time use were prescribed less during pregnancy, while at the same time, an increased prescribing of drugs for pregnancy-related symptoms was seen. For all three categories, the proportion of drugs classified as safe increased during pregnancy compared with the period before and after pregnancy.

The prescription rate covering the 3-year study period was very high, with 97 per 100 women receiving at least one prescription drug. The high prescription rate may reflect the

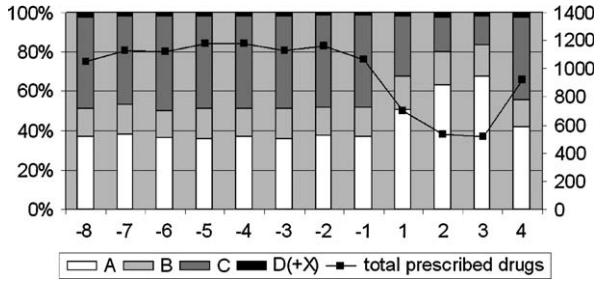

Figure 5. Total number of prescription drugs for chronic conditions (only the prescribed drugs that were categorised as drugs for occasional and short-time use as presented in Table 1were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

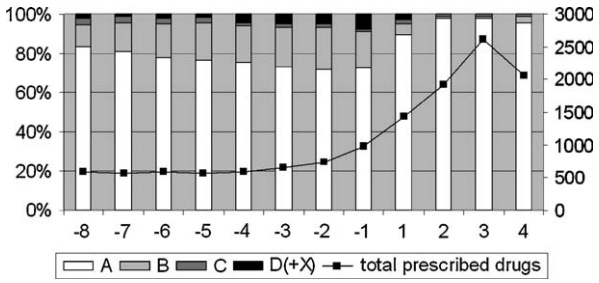

Figure 7. Total number of prescription drugs for pregnancy-related symptoms (only the prescribed drugs that were categorised as drugs for occasional and short-time use as presented in Table 1 were counted) per trimester and the distribution of these drugs according to the pregnancy risk classification.

origin of our study population. To be included in the prescription database, a person had to purchase at least one prescription drug at a participating pharmacy since 1994. In our population, the prescription rate during pregnancy, including vitamins and iron, was 79%. This percentage is somewhat higher than found in a Dutch cohort of women with a low-risk pregnancy (76.5% of the women attending a gynaecologist and 57.4% of the women attending a midwife used medications during pregnancy), but in the latter study, iron supplements were excluded.[16] The prescription rate in this study was high compared with register-based studies in Denmark (44.2%, excluding iron and vitamins),[1] Finland (46.2%)[17] and USA (64%, excluding vitamins and minerals).[18] Higher prescription rates during pregnancy were found in the South West of France (99%, including iron and vitamins)[2] and in Germany (96.4 and 85.2%, including and excluding vitamins, respectively).[4] Several explanations can be given for the differences in prescription rates. The Danish study used a database that did not include prescribed drugs that were not refunded, such as benzodiazepines, many analgesics and antacids, explaining the lower prescription rates. Cultural prescribing differences might also play a role in these variations.

Except for drugs used in diabetes, most drugs for chronic conditions were prescribed less during pregnancy. In the trimester after pregnancy, the prescription rate increased but not to the pre-pregnancy level. Low prescription rates shortly after pregnancy are most likely a result of breastfeeding. For some drugs, such as antidepressants and antipsychotics and antiepileptics, the decrease in prescription rate started before pregnancy. This decrease may indicate precautionary measures by women planning pregnancy, as the safety of these drugs is not established. Several studies have associated the use of antidepressants with adverse pregnancy outcomes such as spontaneous abortions, low birthweight and gestational age.[19,20] From our data, it is not possible to infer whether the decreases are physician driven or woman driven. As the indication for prescription is not known, the possible adverse effects of stopping some of these medications is not known. The prescription rate of antimigraine medication decreased in the second and third trimester of pregnancy, which might be a consequence of less migraine attacks during pregnancy or the use of other analgesics such as paracetamol. Anti-inflammatory and antirheumatic drugs were also rarely prescribed in pregnancy: the use of these drugs is contraindicated in pregnancy and moreover, rheumatic disease activity improves in most women during pregnancy.[21]

The prescription of most drugs for occasional and short-time use decreased during pregnancy. The increase in the prescriptions for antibiotics in the second and third trimester can be explained by urinary tract infections, a complication in pregnancy for which treatment is recommended. The high prescription rate of antibiotics after pregnancy is most likely caused by infections of the breast and uterus. Because antibiotics are also frequently prescribed outside pregnancy, we decided to categorise antibiotics as drugs for occasional and short-time use.

The proportion of class A drugs prescribed during pregnancy is somewhat lower than the proportion found in an other study conducted with the IADB (81.7 versus 86%).[6] This difference can be explained because we restricted our analysis to the drugs that were ordered into the three categories (65.7% of all drugs). In the previous study of the IADB, all drugs were included. The proportion of category A drugs in our study is much higher than found in a Danish study, where 40.9% of all prescriptions during pregnancy were classified as safe (A).[22] We found that 2.4% of all drugs prescribed in the first trimester were harmful drugs. The harmful drugs prescribed in the first trimester for pregnancy-related symptoms were ovulation-stimulating drugs, and for chronic conditions, antiepileptics. Doxycycline, a tetracycline antibiotic, was responsible for the high percentage of harmful drugs for occasional use in the first trimester. Doxycycline may affect the bone and tooth development of the developing fetus and is therefore contraindicated in pregnancy.

The strength of our study was that for all women included in this study, complete data were available on drugs prescribed in the period from 2 years before pregnancy until 3 months after delivery. Because we applied a cohort design comparing the prescription rates during pregnancy with the prescription rates before pregnancy in the same population, selection bias is minimised. Some drug-utilisation studies compare drug use among pregnant women with drug use among nonpregnant women of comparable age. This might introduce bias, since factors related to pregnancy and drug use might be disproportionately present in the two groups. A Finnish study showed that more nonpregnant women had a chronic disease such as epilepsy, rheumatoid diseases, diabetes, hypertension, ulcerative colitis and psychotic and mental disorders when compared with pregnant women of comparable age.[17]

By distinguishing drugs based on their indication, we could demonstrate that the increase in prescription rate during pregnancy is caused by an enhanced prescribing of drugs for pregnancy-related symptoms. Most other drug-utilisation studies that investigated drug-use patterns among pregnant women make no distinction between the indications for drug use.

Although our study was conducted with data from a population-based prescription database, only women with a liveborn child are included. Women with a spontaneous or induced abortion and women whose pregnancy resulted in a stillbirth or whose child did not survive until the first prescription were not included.

Since we have no information on the actual length of the gestation period, the time of conception was estimated

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as 273 days (39 weeks) before birth. The use of a standard gestational period, mostly 270 days, is common in studies using administrative data.[4,17,18] A recent study, comparing administrative data with data from a birth registry, showed that gestational age assumptions can result in a small proportion of misclassification. The extent of potential drug-exposure misclassification was larger for category X drugs in the first trimester of pregnancy.[23] We believe that administrative datasets with estimated gestational age can be useful in research on prescription of drugs during pregnancy. However, in studies evaluating the risk of drugs on birth outcome, precise timing of drug exposure is essential and then administrative datasets alone are insufficient.

In our study, ovulation-stimulating drugs were prescribed in the first trimester of pregnancy, an indication that misclassification has occurred. Prescription of other harmful drugs in the first trimester can also be explained by unawareness of the pregnancy. Although almost 80% of the pregnancies in the Netherlands are planned, a woman mostly does not recognise her pregnancy until the third week after conception.

The prescription rate as defined in this study reflects the prescribing behaviour of physicians and cannot be translated directly into exposure rates. Drugs prescribed for a longer period of time can lead to an underestimation of exposure in the subsequent trimesters. Also, particularly in pregnancy, prescribed drugs are not always taken, leading to overestimation of drug exposure. In a Danish study, only 43% of all drugs dispensed to pregnant women were reported to be taken. Compliance was high for drugs used in chronic diseases but low for drugs used for local or short-time treatment.[24] Furthermore, the prescription database does not include drugs administered in hospitals and OTC drugs. For some drugs, underestimation of exposure may be considerable. The prescription rate of analgesics and antipyretics, for instance, is very low, with approximately 1.5 per 100 women during pregnancy. The number of women who used analgesics during pregnancy is probably much higher because analgesics are freely available in the Netherlands. In a recent study in the USA, where data on maternal drug use were evaluated from two case–control studies of birth defects, at least 65% of the women took paracetamol at some point during pregnancy.[25] Other pregnancy-related drugs such as antacids, laxatives, folic acid and some antiemetics are also available as OTC drugs in the Netherlands.

Although not all drugs prescribed to the study population were ordered into the three categories, we believe that this study is representative for drugs prescribed to pregnant women. The drugs included in the three categories accounted for almost 90% of all prescriptions in the pregnancy period. Drugs not included in the analyses were rarely prescribed.

The use of population-based prescription databases is an important tool to monitor the use of drugs among pregnant women to identify problems. In addition, this individual-level exposure data can serve as a reference for future risk-assessment studies and provide relevant information for education programmes of health professionals as well as for prevention. Although drug use during pregnancy is mostly studied in relation to the occurrence of congenital anomalies at birth, other adverse long-term effects in the offspring, such as developmental delay, may also be associated with maternal drug use in the second and third trimester. In a cohort study in the South West of England, frequent paracetamol use in late pregnancy was associated with an increased risk of wheezing in the offspring at 30–42 months.[26] If maternal drug use can be linked to the prescription of drugs to their children, prescription databases may also be used to screen for certain long-term drug effects.

In conclusion, this register-based study shows that the majority of the Dutch women use drugs during pregnancy. The increase in prescription rate during pregnancy is caused by an increase in prescription rate for drugs used for pregnancy-related symptoms, whereas the prescription rate for drugs for chronic diseases and for occasional and short-time use declines during pregnancy. Also, the prescription of harmful drugs decreases during pregnancy. However, 2.3% of all drugs prescribed for occasional and short-time use in the first trimester were classified as harmful. Therefore, the results of this study argue in favour for a cautious prescribing of drugs to healthy women in the fertile age, in which the prescription of harmful drugs should be avoided as much as possible.

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Appendix 1. Prescription rate per 100 women per trimester* and the results of the chi-square test for trend for all drugs and for the drugs ordered into the three categories

	Trimester												χ^2 test for trend					
													Total period			Pregnancy		
	−8	−7	−6	−5	−4	−3	−2	−1	1	2	3	4	χ^2	*P*	Slope	χ^2	*P*	Slope
All drugs	43.0	43.4	43.3	44.0	44.2	43.0	43.2	43.3	43.6	49.3	60.8	68.0	873.218	0.000	/	320.495	0.000	/
I: Drugs for chronic diseases																		
Drugs used in diabetes (A10)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.6	0.4	2.126	0.145		1.695	0.193	
Corticosteroids, dermatological (D07)	4.7	5.1	4.7	5.1	5.1	4.9	5.2	2.7	3.9	3.6	3.4	4.7	29.701	0.000	\	1.400	0.237	
Corticosteroids, systemic (H02)	0.8	0.7	0.8	0.8	0.8	0.7	0.9	0.7	0.4	0.4	0.4	0.6	14.823	0.000	\	0.000	1.000	
Thyroid therapy (H03)	0.7	0.7	0.7	0.8	0.8	0.8	1.0	0.9	0.9	0.9	0.9	1.0	4.930	0.026	/	0.000	1.000	
Anti-inflammatory and antirheumatic drugs (M01)	6.2	6.4	7.1	7.2	7.4	7.1	7.4	6.7	2.2	0.7	0.3	5.0	407.643	0.000	\	86.643	0.000	\
Antimigraine medication (N02C)	0.8	1.0	0.9	1.0	1.0	0.9	1.0	0.8	0.3	0.0	0.0	0.6	72.332	0.000	\	25.607	0.000	\
Antiepileptics (N03A)	0.3	0.4	0.3	0.3	0.3	0.4	0.3	0.2	0.3	0.3	0.2	0.3	1.844	0.174		0.150	0.698	
Antipsychotics and antidepressants (N05A, excl. N05AB04; N06A)	3.0	3.0	2.9	3.1	3.0	2.9	3.2	2.6	1.9	1.0	0.9	2.1	107.641	0.000	\	17.374	0.000	\
Antiasthmatics (R03)	2.4	2.9	2.7	2.9	2.9	2.6	2.6	2.6	2.4	2.4	2.3	2.1	9.788	0.002	\	0.145	0.704	
II: Drugs for short-time and occasional use																		
Antispasmodic and anticholinergic agents and propulsives (A03, excl. A03FA01)	1.6	1.4	1.5	1.5	1.5	1.6	1.3	1.4	0.9	0.3	0.4	0.7	89.387	0.000	\	15.780	0.000	\
Antidiarrhoeals, intestinal anti-inflammatory/anti-infective agents (A07)	0.6	0.7	0.7	0.7	0.7	0.6	0.7	0.6	0.6	0.5	0.6	1.9	16.933	0.000	/	0.017	0.897	
Antifungals for dermatological use (D01)	2.6	2.3	2.4	2.7	2.1	2.4	2.4	2.1	2.6	2.9	3.2	4.7	44.349	0.000	/	3.579	0.059	
Emollients and protectives (D02)	2.0	2.3	1.9	2.0	2.1	1.6	2.0	1.7	2.1	2.3	2.2	2.7	4.457	0.035	/	0.276	0.599	
Antibiotics and chemotherapeutics for dermatological use (D06)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	16.963	0.000	\	0.644	0.422	
Antiacne preparations (D10)	1.3	1.4	1.1	1.1	1.0	1.0	1.0	1.0	0.8	0.7	0.6	1.2	9.940	0.002	\	6.557	0.010	\
Antibacterials for systemic use (J01)	8.2	8.0	8.5	8.2	9.0	8.2	7.9	8.1	6.3	7.3	8.8	13.3	19.427	0.000	/	24.448	0.000	/
Analgesics and antipyretics (N02B)	2.4	2.5	2.7	2.1	2.1	2.1	2.0	2.1	1.4	1.1	1.1	1.6	69.431	0.000	\	1.743	0.187	
Anxiolytics, hypnotics and sedatives (N05B, N05C)	2.7	2.9	2.5	2.9	3.2	3.0	2.9	2.6	1.2	0.9	1.5	2.4	66.673	0.000	\	1.797	0.180	
Antiparasitic products, insecticides and repellents (P)	0.7	0.7	0.6	1.0	0.9	0.8	0.9	0.7	0.2	0.1	0.3	0.7	22.614	0.000	\	1.074	0.300	
Antihistamines for systemic use (R06, excl. R06AD and R06AE)	2.2	2.2	1.7	1.9	1.8	2.3	2.2	1.8	1.0	0.4	0.3	1.2	109.604	0.000	\	20.800	0.000	\
Ear, eye, nose and throat preparations (S02, S03, S01, R01, R02A, R05)	6.9	6.7	6.9	7.6	6.9	6.5	6.9	6.4	5.2	5.2	4.8	5.2	63.942	0.000	\	1.111	0.292	
III: Drugs for pregnancy-related symptoms																		
Antacids (A02A)	1.1	0.9	0.6	0.5	0.5	0.4	0.5	0.6	2.1	8.5	16.7	0.5	1533.455	0.000	/	692.835	0.000	/
Antiemetics (A03FA01, A04A, N05AB04, R06AD, R06AE)	1.3	1.4	1.6	1.4	1.0	1.3	1.3	1.4	5.8	2.0	1.1	0.8	24.677	0.000	/	208.959	0.000	\
Laxatives (A06)	1.5	1.8	1.3	1.3	1.3	1.5	1.2	1.5	2.4	2.9	2.8	6.9	334.565	0.000	/	2.018	0.155	
Iron preparations (B03A)	3.2	2.4	1.8	1.5	1.2	1.1	1.2	1.3	5.2	21.0	31.5	30.4	6638.584	0.000	/	1208.418	0.000	/
Folic acid and derivatives (B03B)	1.2	1.5	1.6	2.0	2.4	3.1	4.1	6.1	8.6	3.5	4.7	5.2	460.647	0.000	/	79.302	0.000	\
Gynaecological anti-infectives and antiseptics (G01)	2.6	2.5	2.8	2.7	2.5	2.5	2.7	2.7	3.6	6.5	7.2	2.6	168.624	0.000	/	67.139	0.000	/
Gonadotrophins and other ovulation stimulants (G03G)	0.9	1.0	1.3	1.5	1.9	2.5	2.8	4.2	2.4	0.1	0.1	0.0	25.649	0.000	\	168.553	0.000	\

*Trimester −8 to −5 represents the second year before pregnancy, trimester −4 to −1 represents the first year before pregnancy. Trimester 1–3 is the pregnancy period and trimester 4 is the period after pregnancy.

Appendix 2. Total number of prescription drugs per trimester* and the distribution of these drugs according to the risk classification (only the prescribed drugs that were categorised into drugs for chronic conditions, drugs for occasional use and drugs for pregnancy-related symptoms were included)

	Trimester											
	−8	**−7**	**−6**	**−5**	**−4**	**−3**	**−2**	**−1**	**1**	**2**	**3**	**4**
Drugs for chronic diseases												
Total number of prescription drugs	1052	1133	1120	1174	1174	1131	1162	1062	701	536	520	919
Proportion (%) classified as												
A	36.7	38.0	36.2	35.7	36.8	35.9	37.5	36.7	50.4	62.9	67.5	41.8
B	14.5	15.5	14.0	15.5	14.3	15.5	14.1	15.2	17.1	17.4	16.0	13.7
C	46.7	44.5	48.0	47.1	47.4	46.8	47.0	47.1	30.8	17.5	14.6	42.3
D (+X)	2.1	1.9	1.8	1.7	1.4	1.9	1.4	1.0	1.7	2.2	1.9	2.2
Drugs for short-time and occasional use												
Total number of prescription drugs	1632	1628	1587	1651	1636	1553	1573	1497	1166	1109	1186	1805
Proportion (%) classified as												
A	47.9	45.9	48.3	47.6	46.5	45.7	45.5	49.9	60.8	75.1	72.2	58.1
B	32.2	34.3	32.0	33.6	32.4	34.3	35.5	31.5	29.1	18.8	19.4	31.2
C	12.5	13.0	11.8	11.8	12.9	13.1	12.1	12.6	7.8	5.5	8.0	8.6
D (+X)	7.4	6.7	7.9	7.1	8.2	6.9	6.9	5.9	2.3	0.5	0.4	2.1
Drugs for pregnancy-related symptoms												
Total number of prescription drugs	593	573	588	570	594	659	748	975	1433	1913	2612	2051
Proportion (%) classified as												
A	83.0	80.6	77.7	76.7	75.1	73.0	72.1	72.4	89.2	97.6	97.6	95.3
B	11.6	14.7	17.3	18.8	18.7	20.3	21.0	18.5	5.9	1.2	1.3	3.7
C	3.4	3.5	2.7	2.6	1.9	1.8	2.1	1.5	2.1	1.0	1.0	1.0
D (+X)	2.0	1.2	2.2	1.9	4.4	4.9	4.8	7.6	2.9	0.2	0.1	0.0

*Trimester −8 to −5 represents the second year before pregnancy, trimester −4 to −1 represents the first year before pregnancy. Trimester 1–3 is the pregnancy period and trimester 4 is the period after pregnancy.

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